K131544

510(k) Summary for cobas c Bilirubin Total Gen.3

JUL 17 2013

Date prepared: July 17, 2013

Purpose of submission

Roche Diagnostics hereby submits this 510(k) to provide FDA with notification of intent to market a new device named **cobas c** Bilirubin Total Gen.3 reagent. All data in this submission was generated on the **cobas c** 501 analyzer.

This candidate device is a new reagent that was developed by Roche Diagnostics. The previous generation of reagent, Total Bilirubin, was cleared in 510(k) k063543 and serves as the predicate device. The candidate and predicate devices use the same calibrator and controls. Only the reagents differ. This submission presents data to support clearance of this new reagent.

Measurand Total Bilirubin

Type of test Quantitative colorimetric method

Applicant

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Candidate device names

Proprietary name:
cobas c Bilirubin Total Gen.3
Common name:
Bilirubin Total Gen.3

Regulatory information

Product Code	Classification	Regulation	Panel
CIG	Class II	21 CFR 862.1110 (Bilirubin (total or direct) test system)	Clinical Chemistry (75)

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Intended use	In vitro test for the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi **cobas c** systems.
Indications for use	**cobas c** Bilirubin Total Gen.3 is an in vitro test for the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi **cobas c** systems. Measurement of the levels of bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic, hematological, and metabolic disorders, including hepatitis and gall bladder block.
Special conditions for use	For prescription use only
Special instrument requirements	For use on the Roche/Hitachi **cobas c** clinical chemistry analyzer
Candidate device description	**cobas c** Bilirubin Total Gen.3 reagent provides quantitative measurement of the total bilirubin that is present in serum and plasma of adults and neonates. Reagents are packaged in a cassette with two bottles labeled with their instrument positioning, R1 (Reagent 1) and R2 (Reagent 2). R1 contains detergent, buffer, and stabilizers at pH 1.0. R2 is a 3,5-dichlorophenyl diazonium salt: ≥ 1.35 mmol/L.
Predicate device	Roche Diagnostics claims substantial equivalence to the Total Bilirubin reagent on the **cobas c** 501. The reagent was originally cleared in k981632 on the Boehringer Mannheim/Hitachi 917 analyzer, and later cleared in a Special 510(k) k063543 on COBAS INTEGRA and Roche/Hitachi clinical chemistry analyzers. The application to the **cobas c** 501 analyzer was cleared on October 3, 2006 in k060373/A001 following the FDA Policy Document "Replacement Reagent and Instrument Family Policy – 12/11/2003".

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Substantial equivalence - similarities

The following table compares the identical features of the candidate device to the predicate device that was cleared in 510(k) k063543.

Feature	Predicate Device: Total Bilirubin	Candidate Device: Bilirubin Total Gen.3
Intended Use	In vitro test for the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi **cobas c** systems.	Same
Sample Types	Serum and plasma of adults and neonates	Same
Permissible Anticoagulants	Li-heparin K_2-EDTA	Same
Reference Method	Diazo colorimetric method	Same
Calibrator	Calibrator for automated systems (C.f.a.s.) and deionized water as the zero calibrator (C.f.a.s. cleared for use with Total Bilirubin in 510(k) k101456)	Same
Calibration Stability	Recalibrate with each lot and as required following quality control procedures	Same
Reagent Shelf Life Stability	2-8 °C until expiration date	Same
Calibration Mode	Linear regression	Same
Traceability	Standardized against the Doumas manual reference method	Same
Instrument Platform	Roche/Hitachi **cobas c** 501	Same

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Substantial equivalence - differences

The following table compares the different features of the candidate device to the predicate device that was cleared in 510(k) k063543.

Feature	Predicate Device: Total Bilirubin	Candidate Device: Bilirubin Total Gen.3
Reagent Composition	R1: Sulfamic acid 110 mmol/L, Sodium Acetate Buffer 85 mmol/L, Surfactant, and Solubilizer R2: Diazonium ion 3 mmol/L, HCl 100 mmol/L	R1: Detergent, Buffer, and Stabilizers at pH 1.0 R2: 3,5-Dichlorophenyl diazonium salt ≥ 1.35 mmol/L
Reagent On-Board Stability	on-board in use and refrigerated on the analyzers: 5 weeks	on-board in use and refrigerated on the analyzers: 6 weeks
Controls	Precinorm U plus, Precipath U plus, Precinorm U, Precipath U (Controls above cleared for use with Total Bilirubin in 510(k) k042389)	Precinorm U plus, Precipath U plus, PreciControl ClinChem Multi 1[A], PreciControl ClinChem Multi 2[A] [A]These two new controls were cleared for use with Total Bilirubin with 510(k) k102016.

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Substantial equivalence - differences continued

Feature	Predicate Device: Total Bilirubin	Candidate Device: Bilirubin Total Gen.3
Measuring Range	0.10 – 35.1 mg/dL	0.146 – 35.1 mg/dL
Expected Values	Adults and children: up to 1.0 mg/dL Neonates Age of Newborn: Premature 24 hours 1.0-6.0 mg/dL 48 hours 6.0-8.0 mg/dL 3-5 days 10.0-15.0 mg/dL Age of Newborn: Full Term 24 hours 2.0-6.0 mg/dL 48 hours 6.0-7.0 mg/dL 3-5 days 10.0-12.0 mg/dL	Adults: up to 1.2 mg/dL Children with age ≥ 1 month: up to 1.0 mg/dL Newborns: Term and near-term Age of Newborn: 24 hours ≥ 8.0 mg/dL 48 hours ≥ 13.0 mg/dL 84 hours ≥ 17.0 mg/dL
Lower Limits of Measurement□	LDL = 0.10 mg/dL	LoB = 0.10 mg/dL LoD = 0.15 mg/dL LoQ = 0.15 mg/dL

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Test principle

cobas c Bilirubin Total Gen.3 measures total bilirubin by employing the diazo colorimetric method. Total bilirubin, in the presence of a suitable solubilizing agent, is coupled with a diazonium ion in a strongly acidic medium. The color intensity of the red azo dye formed is directly proportional to the total bilirubin and can be determined photometrically.

Precision/ reproducibility

Precision was determined according to CLSI EP5-A2. The study included human sera samples (0.51, 17.7, and 31.8 mg/dL) and two serum-based control samples in two aliquots per run and two runs per day for 21 days.

Here are summaries of the repeatability and intermediate precision data.

Repeatability Summary

Specimen	PCCC1*	PCCC2*	Human Serum 1	Human Serum 2	Human Serum 3
Total Mean (mg/dL)	**0.90**	**3.09**	**0.51**	**17.7**	**31.8**
Within Run Imprecision SD (mg/dL)	**0.02**	**0.02**	**0.01**	**0.10**	**0.14**
Within Run Imprecision CV%	**2.1**	**0.6**	**2.9**	**0.6**	**0.4**
Min (mg/dL)	0.85	3.03	0.46	17.36	31.41
Max (mg/dL)	0.94	3.15	0.55	17.95	32.43

Intermediate Precision

Specimen	PCCC1*	PCCC2*	Human Serum 1	Human Serum 2	Human Serum 3
Total Mean (mg/dL)	**0.90**	**3.09**	**0.51**	**17.7**	**31.8**
Total Imprecision SD (mg/dL)	**0.02**	**0.03**	**0.02**	**0.14**	**0.18**
Total Imprecision CV%	**2.1**	**0.8**	**3.3**	**0.8**	**0.6**
Min (mg/dL)	0.85	3.03	0.46	17.36	31.41
Max (mg/dL)	0.94	3.15	0.55	17.95	32.43

Values that appear in bold type also appear in the labeling.

*PCCC1 = PreciControl ClinChem Multi 1

*PCCC2 = PreciControl ClinChem Multi 2

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Linearity/ assay reportable range

Linearity was assessed according to CLSI EP6-A with one batch of reagent, in one run, and with samples measured in triplicate. Two separate dilution series differing by sample type (serum and plasma) were prepared with thirteen levels for the plasma series and fourteen levels for the serum series. Lithium-heparin was used to prepare the plasma sample series. The highest concentration samples exceed the desired measuring range. The highest concentration samples were created by taking a human serum/plasma sample pool and spiking it with unconjugated bilirubin.

Measuring Ranges that are Supported by the Linearity Data (mg/dL)

	Plasma	Serum
Range tested	0.12 – 39.0	0.12 – 38.9
Range found	0.12 – 39.0	0.12 – 38.9
Recommended measuring range	**0.15 – 35.1**	**0.15 – 35.1**

The first order (linear) regression is significant for both sample types.

Linear Regression Equation for Serum
$y = 1.0021x - 0.0317$ $r^2 = 0.999881$

Linear Regression Equation for Plasma
$y = 1.0014x - 0.0232$ $r^2 = 0.999954$

Traceability and stability

This method has been standardized against the manual test performance using the Doumas method.

The reagent has been evaluated for transport, shelf-life, and open on-board stability.

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Detection limit

LoB, LoD, and LoQ studies were performed based upon CLSI EP17-A2.

LoB Protocol: One blank sample was tested in n=5 with two analyzers with three reagent batches for six runs per day across three days.

LoD Protocol: Five low-analyte samples were measured in singlicate on two analyzers with three reagent batches for six runs per day across three days.

LoQ Protocol: A low-level sample set of nine was measured in singlicate, using three reagent batches on two analyzers for six runs per day across three days. The LoQ is determined based on precision at 20% CV.

The LoB, LoD, and LoQ claims represent the specifications for each.

LoB claim = 0.10 mg/dL
LoD claim = 0.15 mg/dL
LoQ claim = 0.15 mg/dL

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Analytical specificity - interference from endogenous substances

The reagent was evaluated with three endogenous substances, hemoglobin, lipids, and indican for potential interference with the measurement of total bilirubin.

One pool of human serum was spiked with the interferent. A second pool of human serum contained none. The two pools were mixed in different ratios to yield a dilution series with varying concentrations of the interferent.

The endogenous interference data are summarized in the table. Interference was tested at two levels of bilirubin.

	no interference up to	Claim as it appears in the labeling.
Lipemia Level 1	1196 L index	No significant interference up to an L index of 1000.
Lipemia Level 2	1217 L index	
Hemolysis HbA Level 1	946 H index	No significant interference up to an H index of 800.
Hemolysis HbA Level 2	951 H index	
*Hemolysis HbF Level 1	1053 H index	No significant interference up to an H index of 1000.
*Hemolysis HbF Level 2	1047 H index	
Indican Level 1	3.75 mg/dL	No significant interference from indican up to 3 mg/dL.
Indican Level 2	3.75 mg/dL	

*HbF was tested for hemolysis interference in neonates.

All data passed the following acceptance criteria:

Lipemia: $\leq \pm$ 0.10 mg/dL for samples $\leq$ 1 mg/dL or $\leq \pm$ 10% for samples > 1 mg/dL

Hemolysis HbA: $\leq \pm$ 0.20 mg/dL for samples $\leq$ 2 mg/dL or $\leq \pm$ 10% for samples > 2 mg/dL.

Hemolysis in neonates - HbF: $\leq \pm$ 0.10 mg/dL for samples $\leq$ 1 mg/dL or $\leq \pm$ 10% for samples > 1 mg/dL

Indican: $\leq \pm$ 0.10 mg/dL for samples $\leq$ 1 mg/dL or $\leq \pm$ 10% for samples > 1 mg/dL

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Analytical specificity - interference from common drugs

Fifteen commonly used drugs were examined for potential interference on measurement with **cobas c** Bilirubin Total Gen.3 reagent.

Drug interference testing was performed with serum sample pools at two target concentrations of total bilirubin, one at a low concentration of ~ 1.0 mg/dL and the second one at a high concentration of ~ 14.0 mg/dL.

Total bilirubin concentration in all aliquots is measured in triplicate. The mean value among the triplicates for each aliquot is determined. From the mean values, the percent recovery to the initial value (no drug in sample) is calculated.

The table below summarizes the common drug interferences data:

	Drug	Highest Concentration Shown Not to Interfere with BILT3 (drug concentrations in mg/L)
1	Acetylcystein	150
2	Ampicillin - Na	1000
3	Ascorbic acid	300
4	Phenylbutazone	400
5	Cyclosporine A	5
6	Cefoxitin	2500
7	Levodopa	20
8	Methyldopa + 1.5	20
9	Metronidazole	200
10	Doxycyclin	50
11	Acetylsalycilic acid	1000
12	Rifampicin	60
13	Acetaminophen	200
14	Ibubrofen	500
15	Theophylline	100

All data passed the following acceptance criteria:

Difference in recovery to the reference sample: $\leq \pm$ 10%

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Adult method comparison with predicate device

Total bilirubin values for n=131 human sera adult samples were obtained using the candidate reagent (y-axis) to the predicate reagent (x-axis) on the Roche/Hitachi **cobas c** 501 analyzer. Candidate sample concentrations ranged from 0.18 to 30.38 mg/dL, and they were tested in singlicate. The values were regressed using the Passing/Bablok model to produce the following equation.

$$y = 0.959x + 0.091 \text{ mg/dL}$$
$$r = 0.9997$$

Neonate method comparison with predicate device

Total bilirubin values for n=113 human sera neonate samples were obtained using the candidate reagent (y-axis) to the predicate reagent (x-axis) on the Roche/Hitachi **cobas c** 501 analyzer. Candidate sample concentrations ranged from 0.27 to 27.2 mg/dL, and they were tested in singlicate. The values were regressed using the Passing/Bablok model to produce the following equation.

$$y = 0.957x + 0.154 \text{ mg/dL}$$
$$r = 0.9998$$

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Matrix comparison

Lithium-heparin and K_2-EDTA are permissible anticoagulants for use with this reagent because they do not interfere with recovery of total bilirubin. In an internal study, 35 tubes were collected per anticoagulant. Plasma results were compared to serum results and percent recovery was determined. In terms of % recovery. All data passed the following criteria:
For sample concentrations ≤ 0.99 mg/dL, the deviation must be $\leq \pm 0.10$ mg/dL.
For sample concentrations > 0.99 mg/dL, the deviation must be $\leq \pm 10\%$.

anticoagulants	Sample concentration range tested (mg/dL)	Claimed Measuring Range (mg/dL)
Li-Heparin (full)	0.35 – 34.52	0.15 – 35.1
Li-Heparin (half)	0.84 – 31.65	
K_2-EDTA (full)	0.36 – 34.46	
K_2-EDTA (half)	0.80 – 31.18	
Gel Separation Tube	0.36 – 34.40	

In addition, method comparisons with plasma vs serum were calculated with the following results:

Serum vs. Li-heparin P/B: $y = 1.000x + 0.000$, $r = 0.9998$

Serum vs. K_2-EDTA P/B: $y = 0.985x - 0.016$, $r = 0.9999$

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510(k) Summary for cobas c Bilirubin Total Gen.3, Continued

Expected values/ reference range

Adults[1]	up to 1.2 mg/dL
Children with age ≥ 1 month[1]	up to 1.0 mg/dL

Newborns: Term and near-term[2]

Age of Newborn:	
24 hours	≥ 8.0 mg/dL
48 hours	≥ 13.0 mg/dL
84 hours	≥ 17.0 mg/dL

1. Thomas L. Labor und Diagnose. Indikation und Bewertung von Laborbefunden fur die Medizinische Diagnostik. 7th ed. TH-Books Verlagsgesellschaft 2007:259-273.
2. Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004; 114: 297-316.

Conclusion

The submitted information in this premarket notification supports a substantial equivalence decision.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

July 17, 2013

Roche Diagnostics
C/O Lisa K. Klinedinst
9115 South Hague Road
INDIANAPOLIS IN 46250

Re: K131544
Trade/Device Name: cobas c 501 Bilirubin Total Gen. 3
Regulation Number: 21 CFR 862.1110
Regulation Name: Bilirubin (total or direct) test system
Regulatory Class: II
Product Code: CIG
Dated: May 28, 2013
Received: May 29, 2013

Dear Ms. Klinedinst:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Carol C. Benson -S for

Courtney H. Lias, Ph.D.
Director,
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): k131544

Device Name: **cobas c** Bilirubin Total Gen.3

Indications for Use:

cobas c Bilirubin Total Gen.3 is an in vitro test for the quantitative determination of total bilirubin in serum and plasma of adults and neonates on Roche/Hitachi **cobas c** systems. Measurement of the levels of bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic, hematological, and metabolic disorders, including hepatitis and gall bladder block.

Prescription Use ___X___ And/Or Over the Counter Use ____.
(21 CFR Part 801 Subpart D) (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Yung W. Chan -S

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) k131544